Characteristic abnormal signals in medulla oblongata—“eye spot” sign

Four cases of elderly-onset Alexander disease

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Alexander disease (AxD) is a rare neurodegenerative disorder with a prevalence rate of 1 in 2,700,000.¹ Its pathologic characteristics include the formation of cytoplasmic inclusions in astrocytes, called Rosenthal fibers, and white matter degeneration.² The genetic mutation of glial fibrillary acidic protein (*GFAP*)³ is observed in approximately 97% of cases.

In type 2 AxD,¹ which is usually adult-onset, marked atrophy and abnormal signals in the medulla oblongata and cervical cord are characteristic MRI findings.^{3–5} When the bulge of the basilar part of the pons remains and atrophy of the medulla oblongata and cervical cord is marked,⁶ AxD is strongly suspected.

However, there is no clear standard by which to assess atrophy of the medulla oblongata, and it has been speculated that it becomes more difficult to suspect AxD when the degree of atrophy is mild to moderate. We report 4 AxD patients with an onset age older than 50 years in whom characteristic abnormality of the signal intensity of the anterior portion of the medulla oblongata along with mild to moderate atrophy of the medulla oblongata were observed.

The cases represent 4 patients who were suspected to have AxD and referred to Kyoto Prefectural University of Medicine for *GFAP* gene analysis.

Practical Implications

Bilateral abnormal signals of the anterior portion of the medulla oblongata on MRI may be helpful in diagnosing Alexander disease.

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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Figure Brain MRI of the 4 patients

The upper, lower right, and lower left sections of each case show an axial image of the pyramids, an extended image of the medulla oblongata, and a sagittal image, respectively. Symmetrical signal abnormality of anterior and lateral portions was observed in all cases. It resembles the "eye spot" of *Taenaris* in the medulla oblongata with mild to moderate atrophy. The figure of *Taenaris diana* was cited from <http://www.pteron-world.com>.

Case A

Fatigability during walking developed when the patient was 62 years old, gait disturbance was noted and deteriorated at the age of 64, and subsequently speech disturbance and difficulty swallowing appeared. The patient was hospitalized at age 65 with dysarthria, dysphagia, nystagmus, muscle weakness of the extremities (especially the left upper extremity), increased tendon reflexes of the lower extremities, bilateral Babinski sign, mild trunk and limb ataxia, an ataxic and spastic gait, sphincter abnormalities, and obstructive sleep apnea.

Case B

Impending incontinence and dropped head syndrome appeared at the age of 58 years, and trunk ataxia was noted at age 60. Central sleep apnea was observed at the age of 62. Increased tendon reflexes of the right upper extremity, bilateral Babinski sign, dysphagia, trunk and limb ataxia, orthostatic hypotension, sphincter abnormalities, and scoliosis were noted at age 65.

Case C

After undergoing lumbar laminectomy for paraparesis at the age of 60 years, muscle weakness of the bilateral upper extremities and dysarthria appeared. Muscle weakness of the extremities, increased tendon reflexes of the upper extremities, bilateral Babinski sign, dysarthria, dysphonia, and sleep apnea were observed at age 65.

Case D

Dysarthria and spastic gait had gradually progressed from the age of 64. She was hospitalized at age 65, showing tendon reflexes, bilateral Babinski sign, dysarthria, dysphagia, and limb and trunk ataxia.

MRI findings for each case are presented in the figure and the table, and abnormal signals in the anterior and lateral portions of the medulla oblongata were observed in all patients. Abnormal signals in the hilum of the dentate nucleus and periventricular abnormality were noted in cases B and D. Inferior olivary hypertrophy was not detected on MRI.

DISCUSSION

The following have been reported as characteristic MRI findings in patients with type II AxS: (1) progressive atrophy of the medulla oblongata and upper spinal cord with or without hyperintensities on T2-weighted images,^{1,4,5} (2) involvement of the hilum of the dentate nucleus,^{1,4,5} (3) supratentorial periventricular abnormalities in signal intensity and spotty areas of postcontrast enhancement,⁴ and (4) pial fluid-attenuated inversion recovery signal

Table Summary of clinical features and MRI findings of the 4 patients

Patient	A	B	C	D
GFAP mutation	N386S	E210K	R258H	R70W
Sex	M	F	M	F
Age at onset, y	62	58	60	64
Age at diagnosis, y	65	65	65	65
Neurologic symptoms				
Weakness	+	—	+	—
Spasticity/hyperreflexia	+	+	+	+
Dysarthria	+	—	+	+
Dysphagia	+	+	+	+
Nystagmus	+	+	+	—
Ataxia	+	+	+	+
Palatal tremor	—	—	—	—
Autonomic dysfunction	+	+	—	—
Sleep disorder	+	+	+	—
MRI findings				
Atrophy of medulla oblongata	Moderate	Mild	Moderate	Mild
Abnormal signal of frontal and lateral portions of medulla oblongata	+	+	+	+
Involvement of the hilum of the dentate nucleus	—	+	—	+
Periventricular abnormalities	—	+	—	+

abnormality and middle peduncle signal change or enhancement.⁵ The frequency of signal abnormality of the medulla oblongata varies with the age at onset, and it is observed in various subregions, especially in juvenile-onset patients. In the present 4 patients with elderly-onset AxD and mild to moderate atrophy of the medulla oblongata, the low intensity of the lateral portion of the medulla oblongata has the configuration of butterfly wings, and the signal abnormality in the anterior portion of the medulla oblongata resembles the "eye spot" of *Taenaris*. The signal abnormality of the anterior portion on MRI may reflect myelin loss of the bilateral pyramids.⁷ As degeneration of the medulla oblongata progresses, the "eye spot" sign disappears and the frontal portion of the medulla oblongata becomes atrophic, which may reflect cavity change of the pyramids.⁷

Elderly-onset AxD tends to be more indolent, and the degree of atrophy of the medulla oblongata tends to be milder compared to the early-adult-onset form, which develops in the 20s–40s. The characteristic signal abnormality of the anterior portion of the medulla oblongata that we reported, for which we propose the term "eye spot" sign, is considered to be a useful finding indicating AxD in elderly-onset cases.

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STUDY FUNDING

No targeted funding reported.

DISCLOSURES

T. Yoshida receives funding from a Grant-in-Aid for Scientific Research (C) from Japan Society for the Promotion of Science (grant number 24591273) and from a Grant-in-Aid for Challenging Exploratory Research (grant number 24659433). I. Mizuta receives funding from a Grant-in-Aid for Scientific Research (C) from Japan Society for the Promotion of Science (grant number 24591273). K. Saito, Y. Kimura, K. Park, Y. Ito, and S. Haji report no disclosures. M. Nakagawa has received research support from the Intractable Disease Research Grants, from the Ministry of Health, Labour, and Welfare of the Government of Japan, and from a Grant-in-Aid for Challenging Exploratory Research (grant number 24659433). T. Mizuno reports no disclosures. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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